PROCESS FOR THE TREATMENT AND THE PREVENTION OF AIDS AND OTHER DISORDERS INDUCED BY THE LAV/HTLV III VIRUS

The present invention relates to a process for the treatment and the prevention of AIDS and other disorders induced by the LAV/HTLV III virus.

Only two years after the clinical emergence of the acquired immunodeficiency syndrome (AIDS) and the AIDS related complex (ARC), the discovery of the lentivirus responsible for these syndromes has enabled a decisive breakthrough in the knowledge of the disease, i.e. a viral destruction of the pivotal regulatory cell of the immune system, the T helper/inducer (T4) lymphocyte, leading to a progressive and irreversible immunodeficiency.

The AIDS virus (LAV or HTLV III) is an RNA exogeneously transmitted cytopathic non oncogenic lentivirus. The virus binds selectively to the T4 receptor of T4 cells, but cannot be propagated in vitro into monoctyes, T3, T8 and normal B lymphocytes. After entering the T4 cell, the viral RNA is retrotranscripted by a specific viral reverse-transcriptase into unintegrated linear DNA. The major part of the linear DNA is integrated into the cellular genome, each cell containing many copies inserted at random in chromosomal sites, variable from one cell to another (Shaw GM, et al, Molecular characterization of human T-cell leukemia (lymphotropic) virus type III in the acquired immune deficiency syndrome. Science 1984.226: 1165–71).

The natural evolution of the disease can be divided into an immunoactive period followed by an immunodepressed period.

1-The first immunoactive period is characterized by a number of clinical, histological and biological manifestations mimicking autoimmune diseases. This period may be clinically latent or expressed by a PGL, which is initially isolated or associated with systemic symptoms occurring generally after 1 to 3 years. During this period, many features are suggestive of an intensive immune response: (a) the outbreak of the disease, 2 to 4 weeks after the contamination by an influenza-like syndrome with fever, sore throat, macular rash, arthralgies and lymphadenopathy occuring simultaneously with the seroconversion and lasting a few weeks. This initial syndrome is frequently followed by the reappearance or the persistence for months or years of multiple, tender and fluctuating enlarged lymph nodes, specially in the cervical, occipital and axillary areas, with or without splenomagaly (PGL); (b) the explosive follicular hyperplasia of the cortex, paracortex and medullary zones of the lymph nodes with numerous large cleaved and non-cleaved cells, a high mitotic activity, a few plasmocytes and a patchy infiltration of both T4 and T8 cells in equal number; (c) the increase in spontaneous immunoglobulin secretion resulting from a polyclonal activation of B cells, similar to that observed after Herpes virus infections or in autoimmune diseases, such as systemic lupus erythrematous. It is responsible for the normal humoral response against the previously encountered antigens, the increased IgG, IgA and IgM levels, the presence of immune complexes, associated or not with autoimmune thrombopaenia or neutropaenia and more rarely with nephrotic or demyelinating syndromes, the high level of acid-labile α-interferon (IFN) and the low titres of so-called antinuclear antibodies somtimes observed. This polyclonal activation of B cells probably results partly

form a T-independent stimulation of the B-cells by the AIDS virus or by the frequently associated herpes family viruses and partly from the lowering of a T4 inducer/suppressor cell subset.

2-The second period is that of an increasing immunodepression, resulting from the progressive and regular disappearance of the T4 cells. It begins with systemic symptoms, such as fever, extreme fatigability, weight loss and chronic diarrhea. Simultaneously, the PGL vanishes and the follicular hyperplasia gives place to follicular involution with hyalinisation, prominent angiogenesis and persistence of T8 cells, contrasting with a complete depletion of T4 lymphocytes. Sometimes, usually when the number of T4 cells is around 200–300/μl, a Kaposi's sarcoma or a B cell lymphoma develop, perhaps induced by lymphokines such as angiogenic factor or B cell growth factor. Finally, the opportunistic infections of full-blown AIDS occur a few months after the lymph node regression, usually when the T4 cells count has fallen in the range of 0–150/μl.

All immunostimulating or immunoadoptive treatments attempted up to now, natural and IFNs or IL2, thymic hormones and factors, transfer factor, so-called immunostimulating drugs, e.g. isoprinosine, azimexon, tuftsin, bestatin, cimetidine, thymic transplants and HLA matched lymphocyte transfusions or siblings or identical twin bone marrow transplants have completely failed, as underlined in two recent reviews (Gottlieb MS. et al, Immunotherapy of the acquired immune deficiency syndrome, In: Gallin JI, Fauci AS, eds. Advances in host defense mechanisms. New York: Raven Press, 1985; 5: 149–70, and Lotze MT. Treatment of immunologic disorders in AIDS. In De Vita VT, Hellman S, Rosenberg SA. eds. AIDS etiology, diagnosis, treatment, and prevention. New-York: Lippincott JB company, 1985: 235–63).

The present invention is based on a new therapeutic concept, viz the use of cyclosporins known as immunosuppressors.

Thus we have discovered that the administration of a compound selected from cyclosporins to a patient infected with the LAV/HTLV III virus and having a low number of T4 cells induces an increase of the T4 cell number up to a normal number or at least up to a subnormal number. In general this increase is accompanied by a disappearence of adenopathies and general symptoms at least in the patients at an early stage of the disease.

The administration of cyclosporins may be used for the prevention of AIDS in patients infected with the LAV/HTLV III virus before the appearence of the AIDS symptoms, that is patients with no symptoms or patients with ARC.

The administration of cyclosporins may also be used for the prevention of ARC in patients infected with the LAV/HTLV III virus before the appearence of ARC.

In the patients in which AIDS has appeared the administration of cyclosporins should at least induced a regression of the AIDS symptoms (such as Kaposi's Sarcoma) and the prevention of new opportunistic infections.

Thus the invention provides a process for the treatment and the prevention of the acquired immunodeficiency syndrome and other disorders induced by the LAV/HTLV III virus in a patient infected with said virus, comprising administering to said patient an effective amount of a compound selected from cyclosporins.